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Brief communication

Explorative genetic study of *UBQLN2* and *PFN1* in an extended Flanders-Belgian cohort of frontotemporal lobar degeneration patients

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ABSTRACT

UBQLN2 and *PFN1* were recently associated with amyotrophic lateral sclerosis (ALS). We investigated a role for these ALS genes in frontotemporal lobar degeneration (FTLD). We screened 328 FTLD, 17 FTLD-ALS, and 157 ALS patients. Patients originated from Flanders-Belgium except for 26 Bulgarian ALS patients. The frequency of *UBQLN2* and *PFN1* genetic variants in the FTLD patients was low at 0.30% and 0.91% respectively. Moreover, the biological relevance to disease of the variants was questionable. In *UBQLN2*, we identified p.S346C outside of the PXX domain in 1 FTLD patient. Yet, a closely located serine substitution, p.S340I, was observed in a neurologically healthy control individual. In *PFN1*, we observed the previously reported p.E117G mutation in 3 FTLD patients and in 3 control individuals. In the ALS patient cohort, we detected *UBQLN2* variants in 1.27% of patients. These involved 2 novel *UBQLN2* missense mutations, p.S400G and p.P440L, that were also present in unaffected relatives (i.e., the p.S400G carrier's son [70 years] and daughter [65 years]) and the p.P440L carrier's mother (67 years). No mutations were observed in *PFN1*. In summary, we conclude that genetic variations in *UBQLN2* and *PFN1* in a predominantly Flanders-Belgian cohort of FTLD and ALS patients are extremely rare.

1. Introduction

Recent advances in neuropathology and molecular genetics have started to disclose the biological basis for the observed clinical concurrence between frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) (for detailed review see Van Langenhove et al., 2012).

Recently, a series of new genes have been associated with ALS, among which are *UBQLN2* and *PFN1*. Mutations in *UBQLN2*, located on chromosome Xp11.21, cause dominantly inherited chromosome X-linked ALS and ALS-dementia (Deng et al., 2011). Initially, 5 different *UBQLN2* missense mutations within a 12 PXX repeats region were shown to segregate with disease in 5 unrelated

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families (Deng et al., 2011) (Fig. 1A). Moreover, *UBQLN2* pathology was observed in inclusions in spinal motor neurons in a wide variety of ALS patients and in the hippocampus of ALS-dementia patients (with or without *UBQLN2* mutations) (Deng et al., 2011). To date, 9 additional *UBQLN2* mutations have been identified in ALS (Daoud et al., 2012b; Gellera et al., 2012; Synofzik et al., 2012; Williams et al., 2012) (Fig. 1A). Yet, *UBQLN2* mutations were observed to be rare or absent in most ALS patient cohorts (Millecamps et al., 2012; van Doormaal et al., 2012). In addition to ALS, a number of smaller FTLD samples were tested (Gellera et al., 2012; Synofzik et al., 2012). One potential novel *UBQLN2* mutation outside the PXX domain was reported (Synofzik et al., 2012) that was transmitted by the patient's mother without any signs of dementia or motor neuron disease at the age of 81 years, shedding doubt on its biologic relevance to disease (Synofzik et al., 2012).

Exome sequencing of large ALS families identified 2 distinct missense mutations within *PFN1,* located on chromosome 17p13.2, and coding for a 140-amino acid major growth regulator of filamentous-actin. Sequencing familial ALS patients yielded 2 more *PFN1* variants (1%–2% of familial ALS) (Wu et al., 2012) (Fig. 1B). One proposed mutation, p.E117G, was however also observed in low frequencies in control individuals (0.04%–0.09%) (Wu et al., 2012). Except for p.E117G (Fig. 1B), no *PFN1* mutations were reported in other screening studies of ALS or FTLD (Daoud et al., 2012a; Lattante et al., 2012; Tiloca et al., 2012).

In the present study, we aimed to further expand the genetic screening of the ALS genes *UBQLN2* and *PFN1* to an extended cohort of FTLD patients ($n = 328$). We also examined the genetic contribution of these genes in a smaller series of ALS patients ($n = 157$) and FTLD-ALS patients ($n = 17$).

2. Methods

2.1. Study population

Mutation screening of *UBQLN2* and *PFN1* was performed in a total of 328 FTLD, 17 ALS-FTLD, and 157 ALS patients (Table 1). Most of the patients were from Flanders-Belgian origin except for 26 Bulgarian ALS patients. Patients were evaluated and diagnosed according to established clinical criteria, for FTLD according to the Lund and Manchester group criteria (Neary et al., 2005) and for ALS according to the revised El Escorial criteria (Brooks, 2000). All FTLD patients were previously screened for *GRN*, *C9orf72, MAPT*, *VCP*, *CHMP2B, TARDBP, FUS*, *ATXN2*, and *SQSTM1*; all ALS patients for *C9orf72*, *SOD1*, *TARDBP*, *FUS*, *ATXN2*, *ANG*, *VCP*, and *SQSTM1*, and a series of mutation carriers were identified: 27 *C9orf72*, 18 *GRN*, 6 *MAPT*, 2 *VCP*, and 1 *CHMP2B* in FTLD and FTLD-ALS; and 19 *C9orf72*, 2 *FUS*, 1 *TARDBP*, and 1 *ANG* in ALS patients of Flanders-Belgian origin. Bulgarian ALS patients included 4 *SOD1* and 3 *C9orf72* mutation carriers. In addition to patients, matched control individuals ($n = 1131$) were screened for observed *UBQLN2* and *PFN1* variants. Control subjects were selected to have no family history of neuropsychiatric problems, a Mini Mental State Examination score >26, and to be aged within the range of the mean age of onset in the patients ±2 standard deviations. For detailed descriptions of the patient and control cohorts see Table 1.

All research participants or their legal guardian gave written informed consent for participation to the genetic study. The informed consent forms for patient ascertainment were approved by the Ethics Committee of the University and the University Hospital of Antwerp, Belgium.

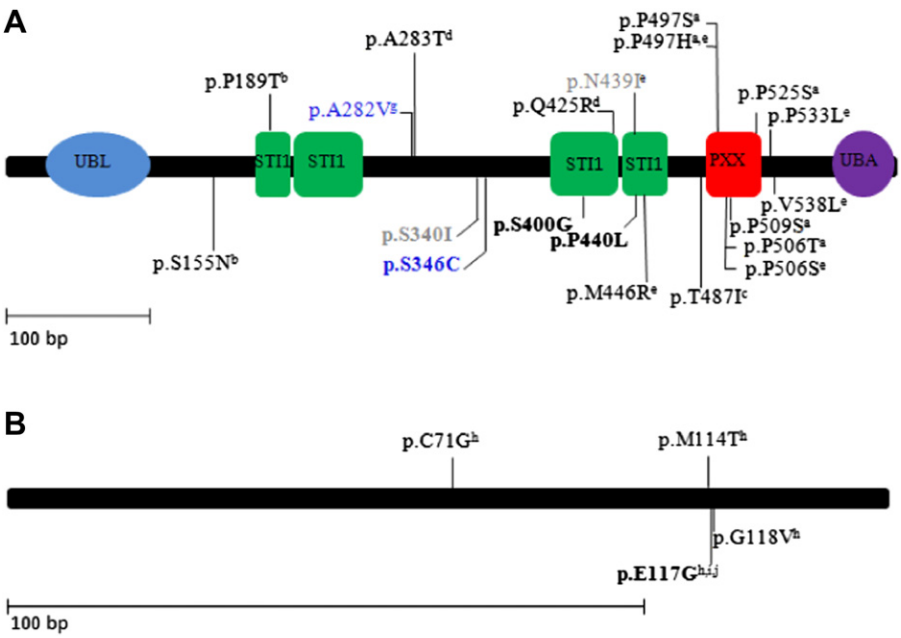

Fig. 1. (A) Predicted structural and functional domains of *UBQLN2* with observed coding variations. UBL (33–103) binds to subunits of the proteasome; STI1, 4 heat shock chaperonin-binding motifs (178–206, 208–247, 379–426, and 430–462); PXX, a 12-PXX repeat region (491–526); UBA (582–620) binds polyubiquitin chains that are conjugated to proteins marked for degradation by the proteasome. Reported mutations are mapped. Observed mutations from the present study are in bold. Coding variants in ALS patients are in black, in FTLD patients in blue, and in control subjects in gray. Mutation in ALS patients reported by [a]Deng et al., 2011, [b]Daoud et al., 2012b, [c]Williams et al., 2012, [d]Synofzik et al., 2012, [e]Gellera et al., 2012, and mutation in an FTLD patient reported by [f]Synofzik et al., 2012, and mutation in a control individual reported by [g]Gellera et al., 2012. (B) *PFN1* with observed coding variations. The observed mutation in FTLD patients and control subjects in the present study is in bold. Mutation in ALS patients reported by [h]Wu et al., 2012, [i]Tiloca et al., 2012, and mutation in a control individual reported by [j]Wu et al., 2012. Abbreviations: ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; UBA, ubiquitin-associated domain; UBL, ubiquitin-like domain.

Table 1
Descriptive characteristics of patient and control cohorts

Family history	Origin	*n*	Age, y[a]	SD, y	Male, *n* (%)
FTLD					
Total	Belgian	328	62	10.55	179 (54.57)
Familial	Belgian	117	61	9.66	63 (53.85)
Sporadic	Belgian	211	63	10.85	116 (54.98)
FTLD-ALS					
Total	Belgian	17	58	11.10	5 (29.41)
Familial	Belgian	6	56	9.96	1 (16.67)
Sporadic	Belgian	11	60	11.88	4 (36.36)
ALS					
Total	Belgian/Bulgarian	157	56	13.64	93 (59.24)
Familial	Belgian	27	54	13.25	19 (70.37)
Sporadic	Belgian	104	59	12.70	57 (54.81)
Familial	Bulgarian	6	60	6.56	5 (83.33)
Sporadic	Bulgarian	20	37	7.18	12 (60.00)
Control individuals					
Total	Belgian/Bulgarian/Gypsy	1131	NA	NA	NA
	Belgian	864	66	10.50	368 (42.59)
	Bulgarian	195	Not available	Not available	Not available
	Gypsy	72	Not available	Not available	Not available

Key: ALS, amyotrophic lateral sclerosis; Familial, positive familial history; FTLD, frontotemporal lobar degeneration; NA, not applicable; Sporadic, no documented familial history.
[a] Mean onset age is given for patients and age at inclusion for control subjects.

2.2. UBQLN2 *and* PFN1 *genetic analyses*

In patients, exonic sequencing was performed of all coding exons in *UBQLN2* (1 exon, 5 overlapping amplicons) and *PFN1* (3 exons, 3 amplicons) according to standard procedures. Observed variations were subsequently tested in control individuals by Sanger sequencing of the affected amplicon. Observed variants were further analyzed in silico by PMUT (Ferrer-Costa et al., 2005) and SIFT (Sim et al., 2012). In case of available DNA of relatives of carriers, cosegregation was tested. Haplotype sharing in patients and control individuals carrying the same *PFN1* variant was tested using neighboring short tandem repeats within 1 Mb up- and downstream of *PFN*. For technical details see Supplementary Methods.

3. Results

We report on a systematic mutation screen of *UBQLN2* and *PFN1* in 328 FTLD patients, 17 FTLD-ALS, and 157 ALS patients. Table 2 provides an overview of the genetic variants and information on the carriers. The clinical presentation of mutation carriers is listed in Supplementary Table 1.

3.1. UBQLN2 *screen*

One *UBQLN2* missense mutation p.S346C that was absent in 864 matched control individuals, was detected in a female FTLD patient in whom mutations in *GRN*, *C9orf72*, *MAPT*, *VCP*, *CHMP2B*, *TARDBP*, *FUS*, *ATXN2*, and *SQSTM* were previously excluded (Fig. 1A). Although p.S346C involves a conserved amino acid residue (Fig. 2), in silico analysis by PMUT and SIFT predicted a neutral effect (Supplementary Table 2). The amino acid substitution p.S346C mutation was not observed in the 1000 genomes project nor in dbSNP. Disease onset age in this patient was 77 years and no familial history of disease was recorded.

In 2 unrelated sporadic ALS patients, 2 different *UBQLN2* mutations, p.P440L and p.S400G, were identified that were absent in 864 matched control individuals and from the 1000 genomes project and dbSNP. These patients were negative for mutations in *C9orf72*, *SOD1*, *TARDBP*, *FUS*, *ATXN2*, *ANG*, *VCP*, and *SQSTM1*. The p.P440L alters a highly conserved amino acid residue (Fig. 2). In silico PMUT analysis estimated that p.P440L is most likely pathogenic, yet p.P440L is predicted to be tolerated by in silico SIFT analysis (Supplementary Table 2). This female patient with onset age of 30 years belongs to the Bulgarian patient cohort ($n = 26$) and had a mixed Gypsy/Bulgarian origin. An additional mutation screen in control individuals of Gypsy ($n = 72$) and Bulgarian origin ($n = 195$) revealed no unaffected mutation carriers. DNA of the parents was available for genetic testing and the p.P440L mutation was also observed in the patient's mother, who at age of 67 years, is still asymptomatic. The p.S400G observed in a female Belgian patient with disease onset age of 78 years, involved a conserved amino acid residue (Fig. 2), yet a neutral effect is predicted by in silico analysis by PMUT and SIFT (Supplementary

Table 2
UBQLN2 and *PFN1* mutations in FTLD and ALS patients

Gene	Mutation	Prevalence	Origin	Age, y[a]	Sex	Family history	Occurrence in matched controls
UBQLN2	c.1019G>T, p.S340I	1/864 Control	Belgian	49	Female[b]	NA	NA
	c.1037C>G, p.S346C	1/328 FTLD	Belgian	77	Female	Unknown	0/864
	c.1198A>G, p.S400G	1/157 ALS	Belgian	78	Female	Sporadic	0/864
	c.1319C>T, p.P440L	1/157 ALS	Bulgarian Gypsy	30	Female	Sporadic	0/267
PFN1	c.350-351AA>GT, p.E117G	3/328 FTLD	Belgian	67	Female	Familial	3/864
				57	Male[c]	Familial	
				79	Male	Unknown	

Key: ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; NA, not applicable.
[a] Mean onset age is given for patients and age at inclusion for control subjects.
[b] No indications of neurodegenerative disease at age 62 years.
[c] Carrier of a pathogenic *GRN* A303GfsX14 mutation.

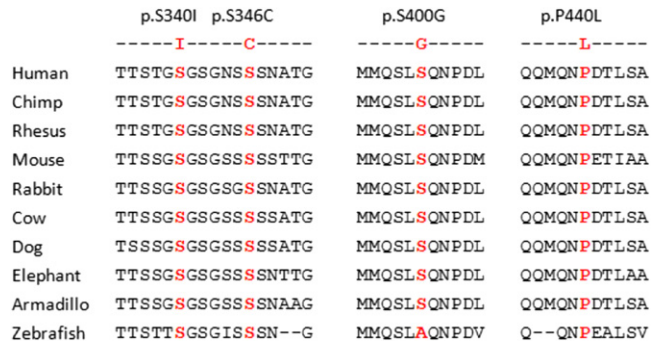

Fig. 2. Evolutionary conservation of *UBQLN2* variations. Mutated amino acids are shown in red.

Table 2). DNA was available from the patient's son and daughter. They both carried p.S400G but were unaffected at the age of 70 and 65 years, respectively.

Finally, in 1 female control individual another missense mutation p.S340I was observed. The p.S340I mutation involves a conserved amino acid residue (Fig. 2), but a neutral effect for p.S340I is predicted by in silico PMUT and SIFT analysis (Supplementary Table 2). Further inquiry about the health status of this person revealed no indications of neurodegenerative disease at the current age of 62 years.

3.2. PFN1 *screen*

No *PFN1* mutations were observed in the FTLD and ALS cohorts that were absent in control subjects. We did detect the previously described p.E117G (Fig. 1B), resulting from a 2-base pair consecutive change (AA to GT) (Tiloca et al., 2012; Wu et al., 2012), in 3 FTLD patients (2 familial FTLD patients and 1 with unknown family history) and in 3 out of 864 matched control individuals (Fig. 1B). The prevalence of p.E117G was not significantly increased in patients (3/328; 0.91%) versus control subjects (3/864; 0.35%) ($p = 0.23$). Mutations in *GRN*, *C9orf72*, *MAPT*, *VCP*, *CHMP2B*, *TARDBP*, *FUS*, *ATXN2*, and *SQSTM* were previously excluded in 2 of the p.E117G FTLD carriers and the third p.E117G carrier with familial FTLD also carried a pathogenic frameshift mutation p.A303GfsX14 in *GRN* (Gijselinck et al., 2008). Haplotype analysis using flanking short tandem repeats indicated that p.E117G in the FTLD patients and control individuals occurred on different haplotypes (data not shown).

4. Discussion

We identified 1 novel patient-specific *UBQLN2* mutation, p.S346C, in a female FTLD patient, that was not previously observed in ALS. However, we detected a similar *UBQLN2* missense mutation, p.S340I, in a female control individual without indications of neurodegenerative disease at age 62 years. Both mutations involve a conserved serine (S) residue in close proximity that do not coincide with any of the predicted functional domains of the Ubiquilin 2 protein (Fig. 1A). In ALS, we detected 2 novel *UBQLN2* missense mutations, p.P440L and p.S400G. Mutation p.P440L affects a conserved proline (P) residue located in the fourth heat shock chaperonin-binding motif (Fig. 1A). In contrast to the initially reported missense mutations that all involved P-residues within a 12-PXX repeat region unique to the UBQLN2 protein, p.P440L is located outside the PXX domain (Fig. 1A) (Deng et al., 2011). Moreover p.P440L was inherited from the patient's mother, unaffected at age 63 years, making it less likely to be pathogenic. The second *UBQLN2* mutation, p.S400G, detected in an ALS patient involved a conserved S-residue located in the third heat shock chaperonin-binding motif. Two of the patient's children aged older than 65 years also carried the mutation without showing any signs of motor neuron disease. Taken together, at present, we have few indications that *UBQLN2* mutations contribute to disease in the FTLD or ALS patients under study. The strongest argument against pathogenicity of the observed variants is the identification of healthy, aged *UBQLN2* mutation carriers (i.e., 1 control individual aged 62 years, an unaffected mother of an ALS patient aged 63 years, and an ALS patient's unaffected son and daughter, aged 70 and 65 years). In contrast, nonpenetrance of *UBQLN2* mutations has been reported (Deng et al., 2011). Moreover, skewed X-chromosome inactivation which is frequently observed in X-linked disorders, could be a possible mechanism underlying reduced disease penetrance in women. For this reason, a potential pathogenic role for missense mutations outside the PXX domain cannot, at present, entirely be excluded.

No *PFN1* mutations absent from control subjects were observed in the Flanders-Belgian FTLD cohort. We did, however, detect the reported p.E117G in 1/117 (0.85%) familial FTLD, 2/211 (0.95%) sporadic FTLD (3/328 or 0.89% of total FTLD), and in 3/864 (0.35%) control individuals, yielding a higher mutation frequency than in previous studies (Tiloca et al., 2012; Wu et al., 2012). Moreover, the familial FTLD patient also carried a pathogenic *GRN* frameshift mutation p.A303GfsX14 (Gijselinck et al., 2008). Our observations that the prevalence of p.E117G is not increased in patients versus control individuals, the concurrence of p.E117G with a pathogenic *GRN* mutation, and the lack of functional evidence compared with other *PFN1* mutants (Wu et al., 2012), suggests that p.E117G is likely a benign polymorphism rather than a disease-causing mutation.

In conclusion, the overall frequency of *UBQLN2* and *PFN1* variations in the Flanders-Belgian FTLD cohort is extremely low, accounting for 0.30% and 0.91% of the FTLD patients, respectively. Moreover, the biologic relevance of the variants to disease remains unclear and needs further investigation. Equally, in the Flanders-Belgian and Bulgarian ALS patients, *UBQLN2* mutations accounted for just 1.27% with questionable pathogenicity. Finally, we observed no *PFN1* mutations in ALS patients.

Disclosure statement

The authors report no conflicts of interest with regard to the reported findings.

All research participants or their legal guardian gave written informed consent for participation in the clinical and genetic studies. The clinical study protocol and the informed consent forms for patient ascertainment were approved by the local Medical Ethics Committees of the collaborating centers. The genetic study protocol and informed consent forms were approved by the Medical Ethics Committee of the University and the University Hospital of Antwerp, Belgium.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.12.007.

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